ORIGINAL RESEARCH

Efficacy of Intravitreal Injection Ranibizumab in Central Retinal Vein Occlusion Patients Presenting With Poor Visual Prognosis

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ABSTRACT

Purpose: To assess the efficacy of intravitreal injection Ranibizumab on visual outcome and macular thickness in patients with Central retinal Vein Occlusion presenting with poor visual acuity.

Place of study: Regional Institute of Ophthalmology, Guwahati Medical College & Hospital

Type of study: Hospital Based Prospective Observational Study.

Duration of study: 12 months

Materials and Methodology: 45 eyes of 45 patients with CRVO were selected prospectively and recruited for intravitreal injection Ranibizumab at baseline and evaluated monthly till 6 months. The patients were given additional ranibizumab for macular edema when required on the basis of optical coherence tomography findings. Patients were evaluated for improvement in Visual acuity, Macular Thickness and complications.

Results: There were 45 eyes of 45 naive CRVO patients who at baseline had a mean age of 57.81 years, a mean Visual acuity of 43.54(±18.26) in Early Treatment of Diabetic Retinopathy letters, and a mean central macular thickness of 546.09(±8.75)µm.At 6 months of follow up ,the mean visual acuity improved to 60.45(±18.96) letters and the central macular thickness decreased to 233.54(±8.75) µm ($p<0.00001$).Change in Visual acuity and macular thickness correlation was not evaluated .

Conclusions: Use of Intravitreal Ranibizumab in cases of CRVO showed improvement in mean Visual Acuity, with low rates of adverse events in 6 months follow up period.

Keywords: Efficacy of Intravitreal Injection Ranibizumab, Vein, Prognosis, Diabetic Retinopathy

Introduction

Central Retinal Vein Occlusion is one of the most common retinal vascular abnormalities in adults and is an important cause of vision loss. [1,2]It has been associated with several underlying causes including age, hypertension, hypercoaguability and diabetic retinopathy. It has now been termed as 'Central Vein retinal Occlusion' because of the presence of a blockage of the vein around the optic nerve head. Leibreich described the clinical appearance of CRVO as 'Retinal apoplexy' in 1854. [3]This was followed by Leber who described it as 'Haemorrhagic retinitis'in 1877. [4]

The pathophysiology of CRVO involves occlusion of the central retinal vein which can subsequently lead to retinal ischaemia which causes increased levels of vascular endothelial growth factor (VEGF).Elevated levels of VEGF causes macular edema and neovascularization, subsequently leading to loss of vision.[5,6]

Introduction of Anti VEGF such as Bevacizumab, Ranibizumab and Aflibercept has shifted the treatment paradigm. This Anti VEGF agent inhibits the effect of Vascular Endothelial growth factor, which is involved in the pathophysiology of macular edema and neovascularisation. Management of CRVO with Anti vascular endothelial growth factor

(Anti-VEGF) therapy has become the current standard treatment procedure.[7,8]

Ranibizumab is an approved Anti-VEGF agent for the treatment of macular edema and neovascularization secondary to retinal vein occlusion worldwide. Many studies have indicated that early, intensive, and individualized treatment with Ranibizumab provides improved Visual acuity (VA) along with underlying disease modification in CRVO.[9]

Our study will prospectively assess the efficacy of intra vitreal injection Ranibizumab in Central vein Retinal Occlusion presenting with poor vision in terms of visual acuity,Macular thickness and complications and with monthly follow up till 6 months on a series of patients attending Regional Institute of Ophthalmology (RIO),Gauhati Medical College and Hospital(GMCH), Guwahati, Assam. GMCH being a tertiary referral centre of North East India, this study will reflect a scenario of success rate in the region of North East India. Since not much study has been done in this area till now, so this study has been carried out in our Institution.

Materials and Methods

This is a hospital based prospective study which was conducted in Regional Institute Of Ophthalmology, Gauhati Medical College And Hospital, during the period of 1st August 2021 to 31st July 2022.

The patients were selected from outdoor as well as indoor .Informed consent was obtained from each of the patients after explaining the purpose of the design.

A total of 45 eyes were included in the study group. All newly diagnosed cases of Retinal vein occlusion after thorough clinical examination and relevant investigations were included in this study

Inclusion Criteria

1. Newly diagnosed cases who did not receive any treatment for CRVO.(naive CRVO)

Exclusion Criteria

1. All patients with Diabetic Macular edema or Proliferative diabetic Retinopathy, advanced age-related macular degeneration OR any patient who had undergone prior intravitreal injection ,laser therapy or surgery.
2. Patients with Dense cataract
3. Patients with Advanced glaucoma
4. Patients with Cardiovascular diseases and Chronic Kidney disease.

Pre Injection Work Up

After the initial screening , cases of Retinal vein occlusion were evaluated with:

- Visual acuity assessment (With and without Pinhole) using ETDRS chart
- Detailed history was taken.
- Intraocular pressure measurement.
- Gonioscopy
- Fundus evaluation
- Spectral Domain Optical Coherence Tomography(OCT -FMT) for assessing :
    i. Central subfield thickness(CST)
    ii. Macular volume
    iii. Presence or absence of sub retinal fluid
    iv. Foveal contour
- Fundus Flourescein Angiography (FFA) wherever necessary.

Investigations included i) Fasting Blood Sugar
ii)Post Prandial Blood Sugar
iii)Glycosylated Haemoglobin (HbA1C)
iv)Fasting lipid Profile
v)Serum Creatinine
vi)ECG

The nature of the study was explained to the patient and/or attendant for their co-operation and selective documentation.

A detailed proforma was made for all the patients meeting the aforementioned criteria.

Data were collected at the first visit after the CRVO onset and reviewed till all sequential follow ups.

Pre Injection Medication

Topical Antibiotic (Moxifloxacin) was started one day prior to the procedure.

Workup for Injection

After selection of patients, they were taken up for Anti VEGF Injection

DOSE: The intravitreal dose of ranibizumab Was 0.5 mg (0.05mL of 10 mg/mL).

After proper anti-septic dressing, topical anaesthesia (Lignocaine 4%) and 5% povidine iodine is instilled into the conjunctival sac and washed off.

The Ranibizumab injection is given 3.5 mm and 4mm from limbus in pseudophakic and phakic eye respectively primarily in the Supero temporal region (other sites are also chosen depending upon the comfortability of the patient).

Mild pressure is applied with tip of cotton bud during withdrawal of the injection to prevent regurgitation of the injected material and topical antibiotic and povidine iodine applied over the injected eye.

This was followed by pad and bandaging of the injected eye and was kept overnight.

Post Injection Management

Oral analgesic is prescribed as and when required.

Dressing was done the next day with topical antibiotic and proper check up was done as per the protocol. Here, Slit Lamp Examination and Fundus Examination was done to rule out any untoward defect. IOP and visual acuity was also measured. Patients were instructed to use the same Topical Antibiotic which was started one day earlier was continued as 1 hourly on First day and 6 times/day for 2 weeks.

Patients are advised to maintain ocular hygiene and to avoid contact with water in the eye where injection was given for 1 week.

Post Injection Follow Up

Patients were followed up and evaluated monthly till the period of 6 months following Anti VEGF injection.

- At each visit Visual acuity assessment, Slit Lamp Examination, Intraocular pressure, Fundus evaluation and OCT-FMT were done and records were documented.
- In Optical Coherence Tomography (OCT - FMT) examination, Central subfield thickness(CST), Macular volume, Presence or absence of sub retinal fluid, Foveal contour were evaluated.

To measure the effectiveness of Ranibizumab age of the patient ,initial best corrected visual acuity (BCVA) and the number of injections administered in the first 6 months were noted.

Statistical Analysis

The data were presented as the mean standard deviation (SD).Statistical differences between pre and post treatment clinical data were assessed using a paired t-test. A p-value of less than 0.05 was considered to be statistically significant.

Results

In this prospective clinical study of 45 eyes which were diagnosed with CRVO during 2021 to 2022 in our institute were treated with intravitreal injection Ranibizumab. Results and data obtained from this study are as follows:

1.AGE

The mean age of CRVO was 57.81 years and the age of presentation in male was 58.22 years and in female was 57.55 years. There were cases of 20 male and 25 cases of female.

Gender	No. of patients	Percentage
Male	20	44.44%
Female	25	55.56%

2.Predisposing Factors

In our study ,we got 25 cases of Hypertension(55.56%), 16 cases of Diabetes mellitus (35.56%) ,4 cases of Hyperlipidemia(8.89%) and 9 cases of Glaucoma (20%).Diabetes mellitus and glaucoma were found to be more commonly associated with CRVO.

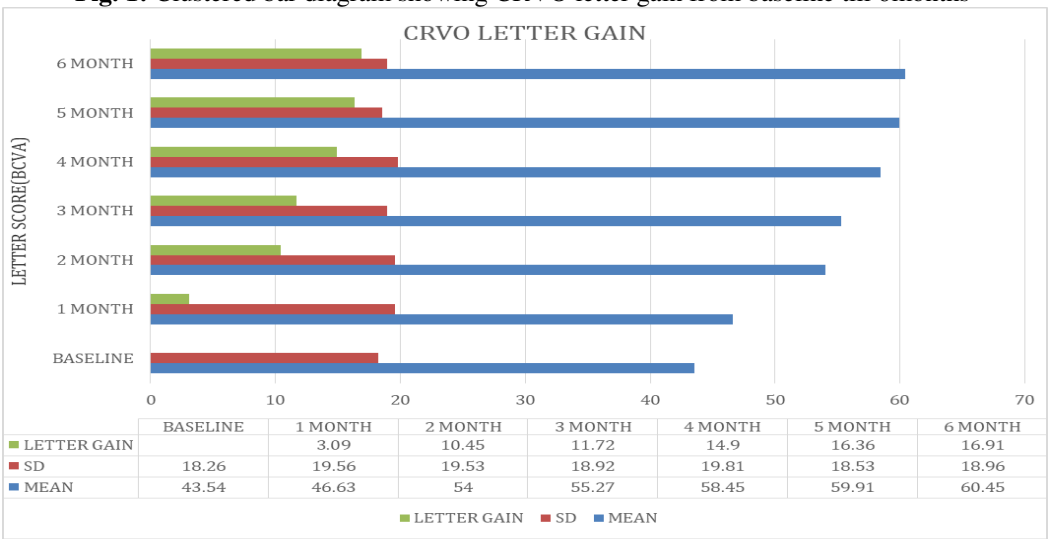
Predisposing factor	No. of Patients	Percentage(%)
Hypertension	25	55.56
Diabetes Mellitus	16	35.56
Hyperlipidemia	4	8.89
Galucoma	9	20

3.Visual Acuity Outcomes

In our study, it was seen that the mean (±SD) BCVA was 43.54(±18.26) letters at baseline and was 60.45 (±18.96) letters at 6 months. From baseline, there was a significant improvement in BCVA by 16.90(±7.03) at 6 months. This was statistically significant ($p<0.00001$).

By 6 months, 45.54% patients gained >/= 15 letters of BCVA and 54.54% of patients were having <15 letters of BCVA.

Fig. 1: Clustered bar diagram showing CRVO letter gain from baseline till 6months



	BASELINE	1 MONTH	2 MONTH	3 MONTH	4 MONTH	5 MONTH	6 MONTH
LETTER GAIN		3.09	10.45	11.72	14.9	16.36	16.91
SD	18.26	19.56	19.53	18.92	19.81	18.53	18.96
MEAN	43.54	46.63	54	55.27	58.45	59.91	60.45

Table 1 :BCVA letter score till 6 months after IVI

4. Change In Central Foveal Thickness (Cft)

Central Foveal thickness was assessed in all OCT images and it was defined as centre point thickness.

There was a significant decrease in CFT after the first IVI of Ranibizumab at 1 month and the decrease in thickness was maintained throughout the study.

The difference in 1 month was statistically significant as were differences at all the subsequent graded assessments($p<0.00024$ for each Ranibizumab injection at each point).The mean (±SD)central foveal thickness decreased from 546.09(±198.48 µm at baseline to 233.54(±8.75 µm) at 6 months.There was a significant reduction in CFT of -312.54 µm at 6 months.

	OCT CFT (in micron)						
	BASELINE	1 MONTH	2 MONTH	3 MONTH	4 MONTH	5 MONTH	6 MONTH
MEAN	546.0909	296	283	269	257.1818	243.8182	233.5455
SD	198.4875	70.43011	57.58993	41.6125	30.15897	14.88501	8.756296
↓CFT	0	-250.091	-263.091	-277.091	-288.909	-302.273	-312.545

TABLE 2 : Decrease in CFT with IVI ranibizumab in CRVO till 6 months

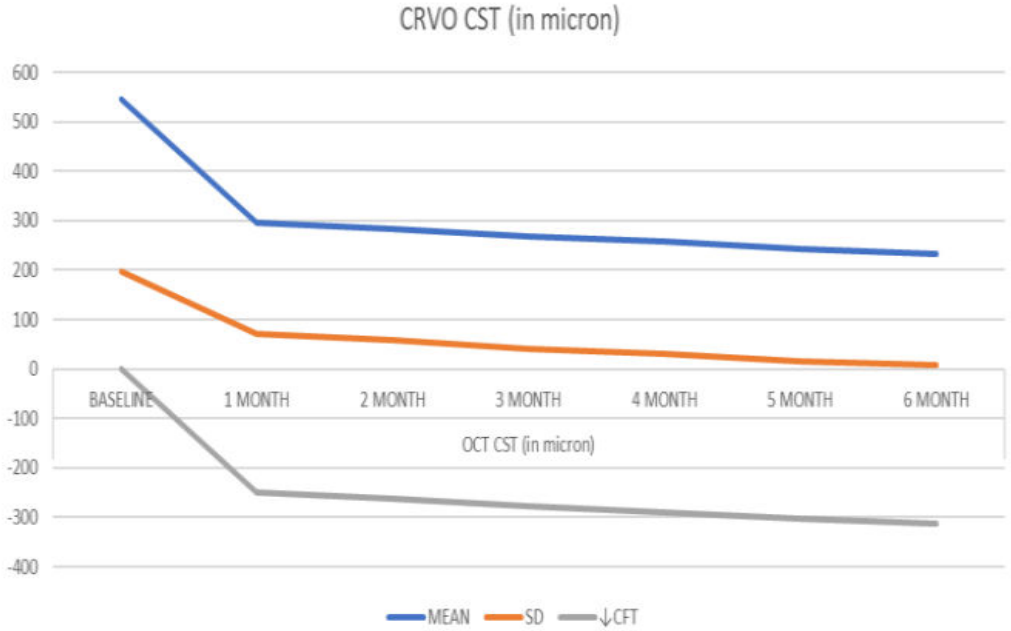


Figure 2: Line diagram showing decrease in CFT after IVI ranibizumab at 6 months.

Complications

During our checkup following injection, we found that 9(20%) cases out of 45 cases of CRVO had Sub conjunctival haemorrhage, which resolved completely within 2 weeks of post injection.18(40%)cases of CRVO had mild to moderate eye pain, some of which required oral analgesics and was controlled with 1 or 2 tablets.5(11.11%) of CRVO patients had developed rise in intraocular pressure following injection which is controlled with short course of anti-glaucoma medications.1(2.2%) case of CRVO also showed mild anterior chamber reaction following Anti VEGF injection which resolved with short course of Topical Steroids. No other patients developed any other ocular side effect.

Among Systemic complications we found that 1(2.2%) out of 45 patients had developed transient rise in Blood pressure. All of them were managed with anti hypertensivedrugs. No other systemic side effects were evident.

COMPLICATIONS	NO. OF PATIENTS	PERCENTAGE(%)
Sub Conjunctival haemorrhage	9	20
Ocular Pain	18	40
Increase IOP	5	11.11
Anterior Chamber Reaction	1	2.2
Raised Blood Pressure	1	2.2

Discussion

CRVO is one of the important sight threatening cause in Modern era. Taking this into consideration, we did this study where a detailed analysis of functional and anatomical outcomes were done in patients with Central Retinal Vein Occlusion who presented with poor visual acuity and who were treated with Intravitreal anti-VEGF injection Ranibizumab.

Other Studies showed that blocking VEGF with intravitreal Ranibizumab has a rapid and beneficial effect on visual function. This effect is due to the reduction in vascular leakage and preventing development of any neovascularisation that is mediated by VEGF.

Change of Visual Acuity in Crvo with Ivi Ranibizumab

In our study, it was observed that the mean (±SD)BCVA in CRVO was 43.54(±18.26) letters at baseline and was 60.45(±18.96) letters at 6 months after treatment with IVI Ranibizumab. From baseline, there was a significant improvement in BCVA by 16.90(±7.03) at 6 months. This was statistically significant($p<0.00001$).The maximum gain in BCVA was achieved during 6 month which was 16.90 letters.

In CRUISE study the Mean (SD) BCVA in CRVO was 48.1(±14.6) letters at baseline and there was a significant improvement in BCVA by 14.9(±13.2) at 6 months.[10]

Brown DM *et al* (2010) found the mean (95% confidence interval (CI) change from baseline BCVA letter score at month 6 was 14.9(12.6-17.2) 0.5 mg Ranibizumab group.[11]

Kinge, Bettina, *et al* (2010) completed the study with 29 patients. After 3 months, BCVA improved by a mean ± standard deviation (SD) of 16 ± 14 Early treatment Diabetic Retinopathy Study(ETDRS) letters in the ranibizumab group (n=15).At 6 months.The mean + SD change in BCVA was 12±20 ETDRS letters in the ranibizumab group.[12]

Hoerauf, Hans,*et al* (2016)found at month 3,improvement in mean (±SD)BCVA was significantly higher in ranibizumab group which is 16.0±13.4 letters. Thus difference between the treatment groups further increased until month 6(raw mean ±SD: +16.96± 13.6 letters for ranibizumab.[13]

Therefore, the effect of IVI Ranibizumab in CRVO on visual acuity in ETDRS chart is comparable to most other studies.

Letter Gain in Crvo with Ivi Ranibizumab

In this study, 45.54% patients gained >/=15 letters of BCVA and 54.54% patients were having <15 letters of BCVA by 6 months.

It is also seen that 36.7%(30-43.30%) patients gained >/= 15 letters of BCVA in CRUISE study[5] ,

Then , Brown DM *et al*(2010)[6] found the percentage of patients who gained >/=15 letters in BCVA was 47.7% (0.5 mg) in the Ranibizumab group at 6 months .

Again, Hoerauf, Hans, *et al* (2016)[8] found a significantly larger proportion of patients who gained >/= 15 letters with Ranibizumab (58.9%) at 6 months.

Henceforth, the improvement of visual acuity in our study following IVI Ranibizumab in CRVO is comparable to most other studies.

Change in Oct in Crvo after IviRanibizumab

There was a significant decrease in CFT after the first IVI of Ranibizumab at 1 month in our studies and the decrease in thickness was maintained throughout the study. The difference at 1 month was statistically significant, as were differences at all subsequent graded assessments ($p=0.00024$ at each time point). The mean (SD) central foveal thickness decreased from 546.09(±198.48) µm at baseline to 233.54(±8.75) µmat 6 months. There was a significant reduction in CFT of -312.54 µm at 6 months.

In CRUISE study, The mean (SD) central fovea thickness decreased from 688.7(±253.1) µm and there was a significant reduction in CFT -452.3(±257.6 µm) at 6 months.[10]

Again, Brown DM *et al* (2010) found CFT had decreased by a mean of 452 µm (0.5 mg) in the ranibizumab group at month 6.[11]

Kinge, Bettina, *et al*(2010) found that the mean ± SD change in CMT was -411±200 µm in the Ranibizumab Group after 3 months and the mean ±SD change in CMT was -304±194 µm with ranibizumab group after 6 months.[12]

Rajagopal, Rithwick ,*et al* (2015)found a mean reduction of 243.8 µm of central foveal thickness in the ranibizumab group after 6 months.[14]

Hoerauf, Hans, *et al* (2016)[8] found mean change of CFT + SD:-376.7 ±274.9 µm from 3rd month to 6th month following IVI Ranibizumab .[13]
Thus the change of OCT in CRVO following IVI Ranibizumab in our study was comparable to other studies.

Conclusion

From our present study we can conclude that intravitreal injection of ranibizumab is found to be excellently efficacious and safe. Best visual acuity outcomes are achieved by treating immediately following diagnosis of CRVO related Macular edema. Intravitreal ranibizumab injection appears to result in significant improvement in BCVA and reduction in macular edema as early as 1 month after 1stinjection.Individualised repeated injections of Ranibizumab also showed promising short term results. Further studies are needed to prove the long term effect of Ranibizumab on patients with Central Retinal vein Occlusion.

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Conflicts of Interest: There are no conflicts of Interest.

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